Cancer Cachexia and Targeting Chronic Inflammation: A Unified Approach to Cancer Treatment and Palliative/Supportive Care

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Abstract Chronic inflammation often acts as a tumor promoter, resulting in aggressive cancerous growth and spread. Many of the same inflammatory factors that promote tumor growth also are responsible for cancer cachexia/anorexia, pain, debilitation, and shortened survival. A compelling case may be made for mounting an attack on inflammation with other anticancer measures at initial diagnosis, with the consequent probability of improving both patient quality of life and survival. High serum levels of the inflammatory marker C-reactive protein or fibrinogen and an elevated white blood cell count correlate with poor prognosis and may be used as a prognostic index to establish the need for nutritional/metabolic intervention. At the author's institution, a concerted effort is being made to screen all newly diagnosed patients with non-small cell lung cancer for the presence of nutritional problems, inflammatory markers, and related symptoms. Interventions include dietary counseling; nutritional and, if warranted, vitamin supplementation; exercise concordant with the patient's physical condition; a prescription for omega 3 fatty acids if inflammation is present, and general symptom management. To establish the value of early nutritional/metabolic intervention, clinical trials are needed that combine measures that combat cachexia and inflammation with first-line chemotherapy in patients who present with weight loss, fatigue, and deteriorating function.

Two major themes dominate the clinical care of patients with advanced cancer: (1) removal or reduction of tumor mass, with subsequent hope for prolongation of life, and (2) palliative/supportive care to control the symptoms associated with cancer. Until recently, most cancer management programs seemingly regarded these two themes as independent elements. Symptoms were regarded as the handmaidens of disease, certainly causing suffering but not related to the course of illness. This view is reflected in our staging systems, which are based primarily on the anatomic extent of tumor growth. Subjective performance status estimates may be included in our assessment of a patient's disease status, but our subjective estimates are often suspect.

The lack of emphasis on symptom studies is disproportionate to their importance to patients and their families. Research in this area is not given a high priority. For example, the number of abstracts on all aspects of cancer nutrition totaled 15 out of 4,917 papers and posters presented at the 2005 Annual Meeting of the American Society of Clinical Oncology (ASCO); in contrast, there were 106 presentations on gemcitabine (Gemzar) alone. No progress on this front was evident at the 2006 ASCO meeting, when the score for nutrition was 10, gemcitabine 86.

Reduced survival following the onset of cachexia is well recognized. Less clearly appreciated is the probability that tumor progression is influenced by the same factors that caused the cachexia. If this is true, efforts to control cachexia may also enhance therapeutic response—an example of where control of symptoms (a principal interest of palliative care) and control of tumor growth (a principal interest of cancer treatment) merge.

The management of cachexia does not lend itself to reductionist approaches; rather, success in managing cachexia will likely depend upon patients having access to programs that stitch together various facets of their care. Included here are early recognition of the problem; correction of secondary causes, such as emotional distress, pain, dyspnea, and a range of potentially reversible gastrointestinal disorders; and a therapeutic platform that incorporates dietary counseling and other nutritional interventions, exercise to maintain muscle mass, and drug combinations that en-

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hance anabolism and reduce muscle proteolysis. A unifying theme linking these constituent parts is the strong evidence that an aberrant inflammatory response to cancer is the principal cause of primary cancer cachexia—the same inflammatory state that stimulates tumor growth and metastases.

Inflammation contributes to the presence and resistance to therapy of many other symptoms often associated with cachexia and sometimes grouped under the appellation "sickness behavior."[1] This constellation of symptoms includes a general sense of illness often identified by the patient as fatigue or loss of energy. Importantly, cancer pain often has an inflammatory component, as may mood changes.

In this article, using inflammation and associated cancer cachexia as a model, we will make the argument for introducing palliative/supportive care at the first diagnosis of a predictably fatal cancer. The presence of malnutrition (so common in the early stages of upper gastrointestinal tumors and lung cancer) can be used as a "stalking horse" for mounting an aggressive, all-out palliative initiative, as analysis and treatment of anorexia/cachexia require a complete review of issues of importance in palliative care. You will not dine well if you are in pain, psychosocially distressed, excessively fatigued, breathless, or suffering from a gastrointestinal problem.

Tumor Inflammatory Response: Friend or Foe?

Frequently one reads of a cancer patient dying after a "brave battle with cancer." Aside from the personal courage of the patient—and the superb partnership of loved ones—this battle has a biologic component. For years, investigators have noted a vigorous cellular immune response to various cancers, ranging from early primaries to large metastatic lesions.

This writer was strongly influenced by a review article by Balkwill and Mantovani in *The Lancet* titled "Inflammation and Cancer: Back to Virchow?"[2] In it, the authors marshal the evidence demonstrating that the cellular infiltrate around tumors commonly does not suppress cancerous growth; rather, it provides "the fuel that feeds the flames." They conclude that "the inflammatory cells and cytokines found in tumors are more likely to contribute to tumor growth progression and immunosuppression than they are to mount an effective host antitumor response. Moreover, cancer susceptibility and severity may be associated with functional polymorphisms of inflammatory cytokine genes, and deletion or inhibition of inflammatory cytokines inhibits development of experimental cancer."

To be sure, our immune response to invasive tumor growth is highly nuanced; certain immune-defense patterns limit tumor progression, even in advanced disease. Nevertheless, immunoreactive cells around the tumor (primarily part of the innate immune reaction*) more likely are acting in malevolent alliance with malignant cells than exerting a defensive posture.[3,4] We are not helped when suppression cues to control the innate response are ineffectual and the system remains in the "on" position. Evidence that this is happening includes the following:

- Tumor-associated macrophages produce angiogenic factors and tissue proteases that promote development of the tumor blood supply and infiltration.[5]
- Stromal factors surrounding a tumor commonly promote an M2 macrophage reaction; ie, one that does not involve an attack on the tumor. Rather, it is associated with a decreased M1 macrophage response, which may interfere with antitumor immunity.[6]
- Tumor tissue is awash in a complex stew of biologic response molecules. Among the more notable of these ingredients are various cytokines, prostaglandins, and leukotrienes.

CYTOKINES

As its name suggests, tumor necrosis factor-alpha (TNF-α) is sometimes an agent that destroys cancer cells; alas, it often switches sides and promotes tumor activity.[7] Indeed, some tumors may produce it as an autocrine growth factor. Production of interleukin-6 (IL-6) is usually associated with a bad prognosis; this agent, like TNF-α, may serve as a tumor promoter.[8,9] Another cytokine whose presence has ominous portent is interleukin-1β (IL-1β). This cytokine is thought to have a major role in cancer anorexia.[10,11]

Multiple other cytokines can influence tumor activity. Probably, unique complex patterns exist for each tumor, some helpful, some not, with a changing balance of cytokine activity. Pending further progress in this fruitful line of cancer research, we may still conclude that TNF, Il-6, and Il-1β responses usually are harmful.

PROSTAGLANDINS AND LEUKOTRIENES

Cell membranes contain polyunsaturated fatty acids (PUFAs) of both the n-6 and n-3 series. Both types can be enzymatically converted into eicosanoids, which are fatty acids that modulate a variety of cell activities, including inflammation.[12] Arachidonic acid, the major membrane PUFA, when acted upon by cyclooxygenase (COX) or lipoxygenase (LOX), will give rise predominantly to proinflammatory prostaglandins and leukotrienes, some of which can stimulate tumor growth. Conversely, the n-3 series membrane PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), give rise to neutral or anti-inflammatory eicosanoids.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Knowledge about the harmful effects of arachidonic acid metabolites has lead to trials of nonsteroidal anti-inflammatory drugs (NSAIDs) as tumor-preventative agents. In addition, a number of current studies are exploring the use of various NSAIDs in combination with chemotherapy. Although these drugs are commonly used as analgesic agents to control pain

* The innate immune-response system is our first-strike, nonspecific response to infection or injury. Dendritic cells, part of this response, will process antigen for cells of the adaptive immune response, which generate targeted responses. These innate immune-cell populations include neutrophils, macrophages, mast cells, and some types of natural killer cells. Adaptive immune cells primarily consist of T and B lymphocytes.

in patients with advanced cancer, only a few studies have been reported in which their tumor and symptom-control properties have been looked at independently. Lundholm's group, for example, uses indomethacin as part of their platform of care; their studies suggest that this drug may enhance the *quantity*, as well as quality, of life possible with control of cachexia.[13–15] A British study on ibuprofen concludes that it may stabilize weight and life quality.[16,17]

OMEGA 3 FATTY ACIDS

Many studies on animal and in vitro tumor models show that omega 3 fatty acids, particularly EPA, can suppress tumors and reduce the adverse effects of a variety of chemotherapeutic agents, notably those of irinotecan (Camptosar).[18–20] A remarkable drop off in antitumor activity, however, characterizes their use in human populations. Phase III trials do not support a role for omega 3 fatty acids in prolonging survival, although debate continues on their efficacy in controlling cancer cachexia.[21] Would omega 3 fatty acids work in combination with other anti-inflammatory agents? Does their poor performance to date in human trials simply relate to a substantial "mouse/human" interface gap? Today, one must resort to that trite phrase, "further studies are needed," to elucidate the potential of omega 3 fatty acids in cancer care.

In summary, chronic inflammation often acts as a tumor promoter, resulting in aggressive cancerous growth and spread. Many of the same inflammatory factors promoting tumors also are responsible for the devastating symptoms that bedevil patients and their families, reducing quality of life and limiting independent function. A compelling case may be made for mounting an attack on inflammation at first onset with other anticancer measures, with the consequent probability of improving both quality of life and survival. A corollary observation: there is now sufficient evidence that the "two solitudes" concept—palliative/supportive care and so-called active cancer treatment—is not supported by cancer biology.

Inflammatory Markers: Relation to Progression and Cachexia

One of the hallmarks of inflammatory states is increased production of hepatic acute-phase proteins. The two proteins most commonly studied are C-reactive protein (CRP) and fibrinogen. CRP's unusual name stems from 1932, when it was identified as a substance induced by streptococcal "C" antigen. A number of cytokines can stimulate the acute-phase reaction; for example, IL-6 activity roughly correlates with CRP levels.[22] Thus, an elevation in CRP level provides indirect evidence of excess inflammatory cytokine production.

In keeping with the adverse effects of proinflammatory cytokines discussed earlier, it is not surprising that raised levels of CRP or fibrinogen have an ominous portent. Numerous studies offer convincing evidence that a high level of CRP at presentation of any advanced cancer translates, regardless of therapy, into a poor prognosis.[23–26] Indeed, in gastroesophageal and renal cancer, it may even foretell the outcome of patients with resectable tumors.[27,28] Although less well documented, a rise in fibrinogen level is also associated with poor outcomes. In melanoma, fibrinogen appears to be a better disease marker than CRP.[29] An elevated fibrinogen level also correlates inversely with survival in lung cancer.[30]

To date, information on inflammatory markers has not been included in the formal staging systems that guide our clinical decisions and offer a common language for interpreting research reports. As the weight of evidence correlating inflammation with poor prognosis is now overwhelming, this situation is surprising. Clearly, the results of small phase II or III studies are skewed by their enrollment of patients with high CRP levels (it is estimated that approximately 40%–60% of patients with advanced lung or upper gastrointestinal cancers will have elevated CRP levels at presentation). We do not yet know, however, whether a high CRP level impacts on initial chemoradiotherapy response or whether the presence of proinflammatory markers should influence decisions on using third- or fourth-line therapies.

ASSESSMENT OF PROGNOSTIC INFLAMMATORY MARKERS

Several studies have combined measurements of inflammatory markers with other indicators in an effort to further refine predictive accuracy. These indicators include:

- *Glasgow Prognostic Score.* Patients with both a raised CRP level and hypoalbuminemia are assigned a score of 2. If only one abnormality is present, a score of 1 is allocated. If no abnormality is present, patients are given a score of 0. In both metastatic breast and non-small cell lung cancer (NSCLC), patients with higher scores have a significantly poorer prognosis.[31,32]
- *CRP plus WBC Score.* At our institution in Montréal, only infrequently do patients present with hypoalbuminemia (a reflection on the average Montréal diet versus the typical Glasgow diet? Fried Mars bars are not popular in Montréal, whereas *foie gras* is.) To hone our prognostic abilities, we coupled white blood cell (WBC) counts with CRP determinations at first presentation (prior to therapy) of our NSCLC patients.[33] Similar to the Glasgow Prognostic Score, a 3-point scale is used. Patients who have both a high CRP level (above 10 mg/L, similar to the Glasgow criterion) and a high WBC count (above 10×10^9 cells/L) are assigned a score of 2. Patients with either abnormality are assigned a score of 1, and those with neither abnormality are given a score a score of 0.

In our initial report, the presence of conventional signs of inflammation, an elevated WBC count, and a raised CRP level at initial diagnosis significantly indicated a worse prognosis than did either a high WBC count or a high CRP level alone. In our updated series, 16 patients (21% of the total) with a score of 2 had a median survival of 3 months, those scoring 1 (45%) had a median survival of 7 months, and those who scored 0 at presentation (34%) had a markedly prolonged median survival of 19 months, confirming our initial findings.

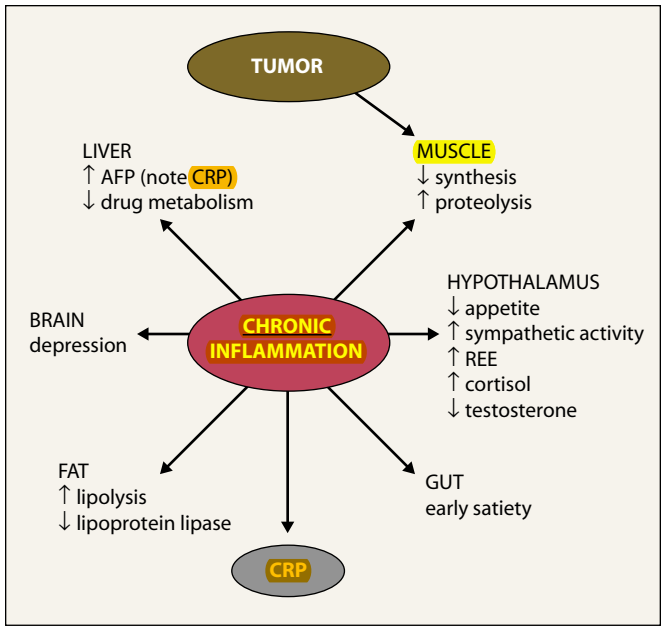

Figure 1 Chronic Inflammation—Systemic Effects

An illustration of the multiple systemic aberrations associated with the chronic inflammatory state.

Abbreviations: AFP = α-fetoprotein; CRP = C-reactive protein; REE = resting energy expenditure

- *Prognostic Inflammatory Nutritional Index (PINI).* Initially framed for evaluation of patients with acute problems (trauma, burns, infection), the PINI weaves CRP and another acute phase protein (alpha-1-acid glycoprotein) with albumin or pre-albumin into a single score.[34] I am not aware of comparison studies on these scales.

Elevated vitamin B_{12} levels coupled with a high CRP level have also been shown to correlate with poor prognosis and have been advanced as a useful prognostic index.[35]

Inflammation–Symptoms–Survival

A common aphorism about pain is, "it won't kill you." It appears, however, that we do not accommodate to chronic pain and associated stress and that it may indeed kill us. Liebeskind[36] mustered the animal evidence that touched on this issue in 1991, clearly showing that pain and stress enhanced tumor growth. Since then, Ben-Eliyahu and colleagues[37,38] have further buttressed Liebeskind observations.

Does reversal of cancer pain in humans enhance survival? Studies are few, but Smith and others[39] offered evidence that intrathecal analgesic therapy may correlate with increased survival of cancer patients, and Lillemoe[40] reported that relief of severe pain by performing a celiac plexus block is associated with prolonged survival of patients with pancreatic cancer.

CANCER ANOREXIA/CACHEXIA

Cancer anorexia/cachexia certainly is a syndrome that kills both directly (at approximately 35% of muscle loss) and indirectly (interfering with respiratory muscle function and the various adverse outcomes secondary to loss of function and a prolonged bed stay). Only a few studies (and these modest in size) have looked at whether reversal of weight loss independently influences patient response to treatment or survival.[41–43] Although the outcomes in these studies are promising, they have not yet generated sufficient interest to mount definitive trials.

Clinicians know that their cachectic patients fare poorly after chemotherapy and experience more severe adverse effects. Chronic inflammation downregulates the cytochrome P450 enzyme system, the key system regulating drug metabolism. Notable inducing cytokines include TNFα, IL-1α, and, to a lesser extent, IL-6—the same trio involved in the onset of cachexia. Downregulation of CYP3A4 will reduce the metabolism of several important classes of chemotherapeutic agents (including the taxanes and camptothecins), thus potentially increasing drug toxicity.[44] In vitro and in several animal systems, inflammatory cytokines have also been shown to interfere with pharmacodynamics; for example, platinum resistance is associated with the presence of IL-6 in an ovarian cancer cell model.[45]

MOUNTING A JOINT EFFORT AGAINST CHRONIC INFLAMMATION

Chronic inflammation is clearly linked to many symptoms and is suspected as a contributory cause in others. The principal villain in the anorexia/cachexia syndrome, chronic inflammation is also a major factor in causing pain[46,47] and, through its effects on muscle, dyspnea and functional loss (Figure 1). Therefore, the supportive care community has an interest in employing therapies that reduce chronic inflammation to alleviate patient suffering. The general oncology community shares this aim but also stresses treatment response and survival, both of which are related to inflammation. Patients and families embrace both of these objectives, and family members in particular may place a higher premium than do health professionals on linking nutrition, exercise, and symptom control with other facets of cancer care.

If our two communities share these values, they will be eager to establish programs that will cover the full gamut of cancer care, starting with the time of diagnosis. Attending physicians and palliative/supportive care specialists may mount joint initiatives to reverse chronic inflammation, recognizing that, in the course of this enterprise, they must identify and master a host of patient problems, some of which are not caused by inflammatory states. For example, only 50% of patients with advanced NSCLC present with elevated serum CRP levels; those who do not will probably live longer, but they will still encounter many problems prior to death.

We have created a model that attempts to match rhetoric with action. For some years, all newly diagnosed patients with lung cancer in the Division of Pulmonary Medicine at Sir Mortimer Davis–Jewish General Hospital in Montréal have been followed from first diagnosis to death by a team made up of pulmonologists and a clinical nurse specialist. The division

has close links with radiation and medical oncologists who attend the weekly tumor board, as well as with members of the hospital's palliative care program.

A Cancer Nutrition–Rehabilitation (CNR) Group was invited to work with the Pulmonary Division and its patients in 2003. This group includes a medical oncologist with an interest in nutrition, a dietitian, and a physiotherapist. New NSCLC patients are now screened for the presence of nutritional and symptom issues. The screen is not burdensome; it consists simply of the Edmonton Symptom Assessment System (ESAS),[48] the Patient Generated Subjective Global Assessment (PG-SGA),[49] and two additional blood tests, a determination of the serum CRP level and, for males, a testosterone profile. (For downloads of these assessment tools, please visit http://www.supportiveoncology.net/journal/0504.html.) Guidelines call for patients to be considered for referral to the CNR clinic—located adjacent to the lung cancer clinic—if they exhibit any of the following characteristics:

- weight loss > 5 pounds within 2 months,
- a PG-SGA score > 4,
- an elevated serum CRP level (> 10 mg/L), or
- an abnormal serum albumin level.

The CNR clinical platform includes dietary counseling; nutritional supplements as indicated (notably, whey protein); an invitation to the patient to partake of an exercise program, the level depending upon the patient's safety and fitness; general symptom management; a prescription for standard-dose vitamin supplements if the degree of malnutrition warrants; and a prescription for omega 3 fatty acids if there is evidence of inflammation. In addition, the clinic provides a milieu for the conduct of clinical trials of nutritional/metabolic interventions combined with chemotherapy.

WHY CLINICAL TRIALS HAVEN'T PROVIDED ANSWERS

What kind of trials should we mount? To date, anorexia/cachexia studies have emphasized the anorexia arm, possibly to the detriment of the cachexia arm, as our most powerful appetite stimulants (corticosteroids and progestational agents) have catabolic effects. Recently, trials that address muscle synthesis/proteolysis have been completed, but their outcomes and interpretation remain somewhat controversial. The value of anabolic steroids and omega 3 fatty acids—agents that assist muscle synthesis and reduce untoward proteolysis—remain unproved in the view of many oncologists. Cachexia is present when muscle anabolism is exceeded by muscle catabolic activity. The poor results observed in previous trials relate, in part, to the advanced state of illness in the study population, but they also stem from the improbability that a single agent would rebalance both arms of the anabolism-catabolism equation. It is surprising, for example, that an anabolic steroid works at all in situations where catabolism is unbridled, for surely a sink won't fill if the plug is removed.

Future trials of interest could include combinations of anti-inflammatory agents and anabolic drugs, with all arms in the studies accompanied by the best nutritional and exercise advice available. This approach may reduce muscle proteolysis and normalize muscle synthesis, thus giving an anabolic steroid the chance to work.

Taking such an approach will require a change in clinical trials' practice, which now prioritizes interpretive studies with narrowly defined inclusion clauses. In their place, pragmatic trials incorporating chemoradiotherapy married with therapies aimed at combating inflammation and associated symptoms may produce outcomes more relevant to all cancer patients.

Cachexia trials are too often relegated to a point in the patient trajectory distant from the time of diagnosis. Enlistment of exhausted, now frail, patients to cachexia trials will not help patients who could benefit from earlier interventions. An anticachexia/anti-inflammation trial should be mounted in concert with a first-line chemotherapy program in patients presenting with weight loss, fatigue, and deteriorating function. Since 60% or more of these patients will eventually become cachectic, you could pick the group without symptoms for study and then look at time to cachexia. Prevention is certainly easier than reversal, even the reversal of "clinically early" disease. The sequential approach—still in vogue—is not in keeping with the patient/family quest for an encompassing envelope of care.

Conclusion

In this article, we have endeavored to present arguments supporting the view that, in addition to social imperatives, there are biologic reasons—notably the association of chronic inflammation with both tumor progress and symptoms—to support a comprehensive care model from the time of diagnosis. In institutions and clinics where these models are in place, clinical trials of optimal therapeutic combinations may be launched more readily. We posit that these trials should center on controlling inflammation. As a result, our patients might well enjoy both a better life and a longer one.

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